



ARTICLE

Breast cancer polygenic risk scores: a 12-month prospective study of patient reported outcomes and risk management behavior

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PURPOSE: To prospectively assess patient reported outcomes and risk management behavior of women choosing to receive (receivers) or decline (decliners) their breast cancer polygenic risk score (PRS).

METHODS: Women either unaffected or affected by breast cancer and from families with no identified pathogenic variant in a breast cancer risk gene were invited to receive their PRS. All participants completed a questionnaire at study enrollment. Receivers completed questionnaires at two weeks and 12 months after receiving their PRS, and decliners a second questionnaire at 12 months post study enrollment.

RESULTS: Of the 208 participants, 165 (79%) received their PRS. Among receivers, there were no changes in anxiety or distress following testing. However, compared to women with a low PRS, those with a high PRS reported greater genetic testing-specific distress, perceived risk, decisional regret, and less genetic testing-positive response. At 12 months, breast screening and uptake of risk-reducing strategies were consistent with current Australian guidelines of breast cancer risk management. Reasons for declining PRS included being unable to attend the appointment in person and concerns over potential emotional response.

CONCLUSION: The outcomes of the study provide insight into women's responses to receiving PRS and highlight the issues that need to be addressed in the associated model of genetic counseling.

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INTRODUCTION

Polygenic risk scores (PRS), typically calculated as the weighted sum of multiple genetic risk variants, have emerged as a potential tool for stratifying individuals into different levels of disease risk [1]. The PRS for breast cancer has been shown to improve stratification of risk in the general population [2] and to successfully identify women remaining at increased risk after exclusion of pathogenic variants in known breast cancer genes, such as *BRCA1* and *BRCA2* (*BRCA1/2*) [3–5]. In the familial setting, PRS can be used to inform risk management strategies for women unaffected by breast cancer, and manage the risk of contralateral disease for previously affected women [6].

Testing for breast cancer PRS is now available in clinical practice, however, important methodological and reporting elements are yet to be addressed, including the effect of ancestry on a PRS [7] and the lack of current guidelines to ensure consistency across laboratories [1, 8]. Furthermore, little is known about how this information impacts patients, as described by patient reported outcomes measures (PROMs), or influences future risk management [9]. Research to date indicates women support a personalized approach to breast cancer risk management based on polygenic information, and initial studies assessing hypothetical

responses [10] or qualitative analysis [11–13] have documented few adverse psychological outcomes.

Prospective data on the implementation of a breast cancer PRS is needed to inform the development of effective risk communication tools and ensure provision of PRS is not associated with adverse psychological outcomes or unwanted health behaviors. This study aimed to assess short (2 weeks) and long-term (12 months) PROMs and describe risk management behavior in women receiving (receivers) or declining to receive (decliners) their personal PRS. The study examined the hypothesis that women receiving a higher PRS would have greater breast cancer-specific distress compared to those with a lower PRS in the short term, but that there would be no persistent differences in patient reported outcomes in the long term.

MATERIALS AND METHODS

Study design and setting

The study protocol, description of consultations, and uptake of the PRS have been published previously [13–16]. Women were recruited from the Variants in Practice (ViP) study, in which genotyping of 62 breast cancer-associated single-nucleotide polymorphisms (SNPs) was performed

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for ~3,700 women and a PRS and corresponding relative risk (RR) for breast cancer were calculated (Supplementary methods 1) [12]. Women from families with no identified pathogenic variant in a breast cancer risk gene on comprehensive testing were eligible to participate, including women who were either affected or unaffected by breast cancer. A total of 400 women meeting these criteria from either end of the PRS distribution in the ViP cohort were selected for this study, i.e., the women with the highest and lowest assessed breast cancer risk based on their PRS. Eligible women were mailed the study information and invited to receive their PRS. Of the 400 women invited, 200 had a PRS associated with an increased breast cancer risk ($RR \geq 1.21$; termed PRS+) and 200 no change/reduced cancer risk ($RR < 1.21$; termed PRS-). The study was approved by the Human Research Ethics Committee at participating sites (HREC/16/PMCC/2 and H0016395).

Sample size and power

The final enrollment for the study was less than the projected recruitment ($n = 215$ receivers) [14] and did not meet the previously calculated power to investigate an interaction between the PRS and disease status. Consequently, this analysis was omitted and a post hoc power calculation was conducted. For a two-sided test based on a 5% significance level, our sample size of 153 receivers who completed the survey at 2 weeks had a greater than 90% power to detect a seven-score difference in the primary psychological outcome of breast cancer anxiety, as measured by the Impact of Event Scale (IES) (SD 14, range 0–75) between PRS+ and PRS- women. This difference is considered a medium effect size [17], as well as being clinically significant in the context of measuring psychological outcomes [18].

Disclosure of the PRS

Women received their PRS at an in-person appointment with a genetic health professional (e.g., clinical geneticists, genetic counselor, clinical oncologist) [16]. Consultations included the disclosure of, and discussion about, the implications of the PRS. A graphical representation of the participant's PRS, including RR of breast cancer compared to the Australian general population (Supplementary Fig. 1) was provided to participants, along with a visual representation of their lifetime absolute breast cancer risk (Supplementary Fig. 1). Most clinicians also provided a verbal description of the PRS category (low, moderate, high) and the breast cancer RR based on the PRS. However, few clinicians described the risk as an absolute figure [16]. Given the research nature of the PRS, clinicians were instructed to offer risk management advice that continued to emphasize their personal and family history of breast cancer.

Data collection

Receivers completed three questionnaires: at study enrollment (baseline), two weeks after receiving their PRS (short-term), and 12 months post receipt of results (long-term) (Supplementary Fig. 2). Decliners completed the baseline survey and a questionnaire 12 months post enrollment. The study questionnaires included the IES [19], Hospital Anxiety and Depression Scale (HADS) [20], perceived risk of breast cancer [21], knowledge of familial breast cancer and PRS [22, 23], the Multidimensional Impact of Cancer Risk Assessment (MICRA) [24], and Decision Regret Scale (DRS) [25]. Likert and open-ended questions captured reasons for declining PRS (Supplementary Table 2) [21]. Self-reported data on breast screening (date of last screening and screening modality) and uptake of risk-reducing strategies (bilateral mastectomy and risk-reducing medication) were also collected [26]. Data collection occurred from August 2016 to December 2019.

Analysis of the impact of receiving PRS on PROM over time

Internal consistency was calculated using Cronbach's alpha for each PROM (Supplementary Table 1). For analysis, receivers were stratified based on whether they received a PRS+ or PRS- result and their personal history of breast cancer (affected and unaffected).

A linear mixed model assessed impact of the PRS on PROMS over time. Interactions between time and the PRS category were considered and removed from the model if $p > 0.05$. For all models, a diagonal covariance structure was used, and disease status was included to account for the potential effects of personal breast cancer history. Other stressful life events that may affect psychological wellbeing [27] were also included in the analysis of the IES, HADS, and MICRA.

Uptake of risk management behaviors

Risk-reducing strategies were compared between baseline and 12-month follow-up to determine uptake during the study period. Logistic regression was used to assess the effect of the PRS on breast screening at 12 months post result. Logistic regression was conducted between predictor variables (PRS, disease status, number of first- and second-degree relatives with breast cancer, age, education level and previous attendance to genetics clinic) and the outcome of reported breast screening at 12 months (i.e., breast mammography, ultrasound, and/or magnetic resonance image [MRI]). Women's age was dichotomized (< 40 years, ≥ 40 years) to coincide with the age women are eligible for publicly funded mammographic screening in Australia, in the setting of family history of breast cancer [28]. Variables where $p < 0.25$ in univariate analyses were included in the multivariate model. A backwards elimination strategy was employed where $p < 0.05$ was considered statistically significant.

Analysis of decliners PROMs and comparison to receivers

Mean differences in IES and HADS scores between receivers and decliners at 12 months were assessed using an analysis of covariance (ANCOVA), adjusted for IES and HADS scores measured at baseline. An independent sample *t*-test was used to assess mean differences in decisional regret between receivers and decliners. Descriptive statistics were used to describe the frequency of agreement for reasons to not receive PRS, and content analysis was used to evaluate responses to open-ended question regarding additional reasons to not receive their PRS. All statistical analyses were performed using SPSS version 25 [29].

RESULTS

Participant characteristics

Of the 400 women invited to the study, 208 (52.0%) consented to participate and completed the baseline questionnaire, 184 (46.0%) did not participate, and 8 (2.0%) were deceased [15]. Of the participants, 165 (79.3%) received their personal PRS and 43 (20.7%) declined (Supplementary Fig. 2) [15]. The mean age of the cohort at baseline was 52.3 years (SD = 13.1). Most women had at least one daughter (57.8%), completed a bachelor's degree (53.1%), and were born in Australia (87.4%) (Table 1). For affected women, the mean age of their first breast cancer diagnosis was 45.1 years (SD 11.5, range 24 to 75 years). Among receivers, 104 (63%) were categorized as PRS+ and 61 (37.0%) as PRS-. The mean breast cancer RR generated from the PRS was 0.7 (SD 0.2, range 0.2 to 1.1) for PRS- women, and 2.2 (SD 0.6, range 1.2 to 3.8) for PRS+. Stratified by personal history, the mean breast cancer RR was 1.8 (SD 1.0) for affected women and 1.4 (SD 0.7) for unaffected women (Supplementary Fig. 3). One woman had a personal history of ovarian cancer, and 22 had a family history on ovarian cancer in a first or second-degree relative.

Retention rate at 12 months was 60.5% for decliners and 87.3% for receivers (Supplementary Fig. 2). There were no significant differences in age, education level, disease status, perceived risk, knowledge of familial breast cancer, general depression and anxiety (HADS), or breast cancer-specific distress (IES) at baseline between participants who were retained and those lost to follow-up. However, receivers were significantly more likely to complete the study compared to decliners, $\chi^2(2, n = 208) = 17.5, p < 0.001$.

Recall of the PRS received

Recall of the verbal description of the PRS category was high. At 12 months, most women (90.8%, $n = 129$) correctly recalled the verbal description of their PRS category (high or low). Four women could not recall their PRS category, and five incorrectly reported they received a low PRS when they had received a high PRS (all had a breast cancer RR > 2). Finally, three women who received a high PRS responded that they did not receive a definite result.

Table 1. Demographic and clinical characteristics of total sample ($n = 208$).

Demographic characteristic	PRS ⁺ , n (%)	PRS ⁻ , n (%)	Decliners n (%)	Total sample, n (%)
Age (years)				
8–29	3 (2.9)	3 (5.0)	2 (4.7)	8 (3.9)
30–39	16 (15.5)	9 (15.0)	3 (7.0)	28 (13.6)
40–49	30 (29.1)	14 (23.3)	10 (23.3)	54 (26.2)
50–59	28 (27.1)	14 (23.3)	15 (34.9)	57 (27.7)
60–69	21 (20.4)	12 (20.0)	6 (14.0)	39 (18.9)
>70	5 (4.9)	8 (13.3)	7 (16.3)	20 (9.7)
Has daughters				
Yes	55 (52.9)	33 (54.1)	32 (74.4)	120 (57.7)
Employment status				
Employed	74 (72.5)	36 (59.0)	26 (60.4)	136 (66.0)
Occupation health care professional				
Yes	13 (12.9)	7 (11.5)	6 (14.3)	30 (14.7)
Marital status				
Married/ de facto	71 (68.9)	38 (62.3)	33 (76.7)	142 (68.6)
Education level				
Bachelor and above	60 (58.3)	36 (59.0)	14 (32.6)	110 (53.1)
Birthplace				
Australia	87 (84.5)	55 (90.2)	39 (90.7)	181 (87.4)
Language spoken at home				
English	100 (98.0)	59 (96.7)	41 (95.3)	200 (97.1)
Total number of FDR and SDR diagnosed with breast cancer				
0	15 (14.6)	0 (0.0)	7 (16.3)	31 (15.0)
1	25 (24.3)	15 (24.6)	16 (37.2)	63 (30.4)
2	33 (32.0)	23 (37.7)	9 (20.9)	64 (30.9)
3+	30 (29.1)	13 (21.2)	11 (25.6)	49 (23.8)
Attended genetics clinic in the past				
No	26 (25.2)	18 (29.5)	22 (51.2)	63 (30.4)
Yes	67 (65.0)	39 (63.9)	19 (44.2)	128 (61.8)
Unsure	10 (9.7)	4 (6.6)	2 (4.6)	16 (7.7)
Personal history breast cancer				
Affected	54 (51.9)	30 (49.2)	21 (48.8)	105 (50.5)
Unaffected	50 (48.1)	31 (50.8)	22 (51.2)	103 (49.5)

FDR first-degree relatives, SDR second-degree relatives.

Impact of receiving PRS on PROMS over time

Breast cancer-specific distress and anxiety (IES) and general anxiety and depression (HADS). At baseline, the mean IES score for all receivers was 9.5 (SD 13.9), of a total of 75, indicating mild distress and anxiety related to breast cancer risk (Table 2) [19]. Similarly, there was mild general anxiety and depression in this population (M 7.8, out of 21, SD 5.5) (Table 2) [20]. Over the course of the study, individual IES and HADS scores did not change and the PRS result received had no effect (Table 3). However, affected women reported an IES score an average of 1.3 units higher ($p < 0.001$) than unaffected women at all time points; mean score at baseline 13.4 (SD 15.4) and 5.9 (SD 11.0), respectively. Affected women also

reported a HADS score on average 2.3 units higher than unaffected women at all time points ($p < 0.001$); mean score at baseline 8.4 (SD 6.1) and 7.1 (SD 4.5), respectively. Those who reported more stressful life events at 12 months also reported significantly higher IES ($p = 0.004$) and HADS scores ($p < 0.001$).

Breast cancer perceived risk. The mean breast cancer perceived risk score at baseline was 51.7 (SD 24.0), on a scale of 0 (no chance) to 100 (will definitely develop breast cancer) (Table 2). Compared to baseline, there was a significant decrease in perceived risk at two weeks ($p = 0.023$) and 12 months ($p = 0.030$) (Table 3). The size of this effect was dependent on the PRS received, with PRS⁻ women reporting significantly lower perceived risk at 12 months (M 41.0, SD 23.9) when compared to PRS⁺ women (M 54.8; SD 25.2) ($p = 0.023$). Affected women also reported a higher score than unaffected women, mean baseline scores 54.1 (SD 24.7) and 49.3 (SD 23.1), respectively ($p = 0.022$).

Knowledge of familial breast cancer and PRS. At baseline, the mean knowledge score was 6.8 (out of 10, SD 1.8). Compared to baseline, knowledge scores were on average 0.5 units higher at two weeks, representing a very small, but significant increase in familial breast cancer knowledge ($p = 0.023$) (Table 3). This effect was not dependent on the PRS received or affected status. Despite this increase, further evaluation of individual items identified that knowledge of specific elements remained low for all receivers (Supplementary Fig. 4). At baseline, only 7.3% of receivers correctly identified that the breast cancer PRS was not associated with increased ovarian cancer risk. At 12 months, 13.5% of participants were able to correctly answer this question, indicating that most women continued to believe the breast cancer PRS was associated with ovarian cancer risk. Among those with a family history of ovarian cancer ($n = 22$), 10 completed the 2-week survey, of whom 5 correctly answered that their breast cancer PRS could not be used to inform ovarian cancer risk. This knowledge remained consistent at 12 months for women in this group.

Genetic testing-specific response (MICRA). At two weeks, the mean genetic testing-specific distress was 3.4 (out of 30, SD 5.0). Distress was on average 1.6 units greater in PRS⁺ women compared to PRS⁻ ($p = 0.004$) (Table 3). Similarly, distress in affected women was on average 1.8 units higher than unaffected; mean score at two weeks 4.5 (SD 4.8) and 2.3 (SD 5.0), respectively.

The mean genetic testing-specific uncertainty at two weeks was 7.2 (out of 45, SD 6.9) (Table 2). The PRS result had no effect on this outcome, but uncertainty was on average 3.6 units higher in affected women than unaffected ($p < 0.001$); mean 9.5 (SD 6.6) and 4.8 (SD 6.3), respectively. Higher distress and uncertainty were also reported by those with greater stressful life event score at 12 months (distress: $p = 0.023$, uncertainty: $p = < 0.001$). Over the course of the study, individual distress or uncertainty scores did not change, with the differences identified sustained at 12 months.

At two weeks, the mean positive experience score was 9.7 (out of 20, SD 5.4), indicating some positive response to receiving the PRS (Table 2). Positive response was on average 4.3 units lower in PRS⁺ women compared to PRS⁻ ($p < 0.001$). Between 2 weeks and 12 months, there was a 4.1 unit decrease in positive response ($p < 0.001$) (Table 3). This change was not dependent on the PRS received, indicating both PRS⁺ and PRS⁻ women reported lower positive experiences by 12 months. Personal history of breast cancer and stressful life events did not significantly affect this outcome.

Decisional regret over receiving PRS. Most receivers (57.4%) reported no regret (score = 0/100) regarding the decision to receive their PRS at 2 weeks and these scores did not change over the course of the study (Table 3). On average PRS⁺ women

Table 2. Mean psychological outcomes for receivers, decliners, and total ($N = 204$).

Measure	Baseline		2 weeks		12 months	
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)
IES (range: 0–75)						
PRS ⁺	103	8.9 (13.4)	96	11.4 (14.2)	92	11.3 (14.0)
PRS ⁻	61	10.6 (14.4)	57	10.6 (13.3)	52	13.1 (17.5)
All receivers	164	9.5 (13.9)	153	11.1 (13.9)	144	11.9 (15.3)
Decliners	40	9.3 (14.0)	-	-	25	8.4 (12.2)
HADS (range: 0–42)						
PRS ⁺	104	8.4 (5.8)	96	6.7 (6.2)	92	6.9 (6.0)
PRS ⁻	61	6.7 (4.8)	57	6.7 (5.6)	52	6.9 (5.7)
All receivers	164	7.8 (5.5)	153	6.7 (5.9)	144	6.9 (5.9)
Decliners	42	7.5 (5.5)	-	-	25	6.7 (5.5)
Knowledge (range: 0–10)						
PRS ⁺	104	6.9 (1.8)	95	7.4 (1.7)	92	7.3 (1.8)
PRS ⁻	62	6.6 (1.9)	58	6.8 (2.0)	52	7.1 (1.6)
All receivers	165	6.8 (1.8)	152	7.2 (1.8)	144	7.2 (1.7)
Perceived risk (range: 0–100)						
PRS ⁺	100	51.8 (25.0)	90	49.2 (27.3)	79	54.8 (25.2)
PRS ⁻	59	51.3 (22.3)	57	40.7 (27.8)	49	41.0 (23.9)
All receivers	159	51.7 (24.0)	147	45.9 (27.7)	128	49.5 (25.5)
MICRA distress (range: 0–30)						
PRS ⁺	-	-	96	4.1 (5.6)	91	3.1 (4.4)
PRS ⁻	-	-	58	2.1 (3.5)	52	1.7 (3.9)
All receivers	-	-	153	3.4 (5.0)	143	2.6 (4.3)
MICRA: uncertainty (range: 0–45)						
PRS ⁺	-	-	96	8.1 (7.3)	91	6.3 (6.6)
PRS ⁻	-	-	58	5.5 (5.7)	52	5.4 (6.9)
All receivers	-	-	153	7.2 (6.9)	143	5.9 (6.7)
MICRA: positive experience (range: 0–20)						
PRS ⁺	-	-	96	8.1 (4.7)	91	5.3 (5.0)
PRS ⁻	-	-	58	12.5 (5.4)	52	8.3 (7.2)
All receivers	-	-	153	9.7 (5.4)	143	6.4 (6.0)
Decision regret (range: 0–100)						
PRS ⁺	-	-	96	7.9 (13.3)	90	10.8 (16.0)
PRS ⁻	-	-	55	4.6 (8.3)	51	6.7 (13.3)
All receivers	-	-	151	6.7 (11.8)	141	9.3 (15.1)
Decliners	-	-	-	-	21	37.9 (16.2)

HADS Hospital Anxiety and Depression Scale, IES Impact of Event Scale, MICRA Multidimensional Impact of Cancer Risk Assessment, PRS polygenic risk score.

reported a score 3.4 units higher than PRS⁻ women ($p = 0.031$). However, these scores were still within the range of minimal regret (Table 2). There was no effect of personal history of breast cancer on this measure.

Risk management behavior

Risk-reducing strategies ($n = 208$). In this cohort of women from breast cancer families, risk-reducing measures were common at baseline: 35 women reported having a bilateral mastectomy, including one unaffected individual (Table 4). Of the four women who had undergone bilateral mastectomy at 12 months, three

were receivers and one decliner, and all had a personal history of breast cancer with at least one of the following features: young age of diagnosis (<40 years), bilateral disease, and increased risk PRS. Of the 43 women taking tamoxifen at baseline, 41 (95.3%) were taking it as adjuvant therapy and two unaffected women as prevention (4.7%). At 12 months, six women began taking risk-reducing medication and uptake of these strategies was limited to affected women (Table 4).

Breast screening ($n = 158$). Based on the date of their last reported breast screen, women who had not undergone a

Table 3. Standardized beta weights (confidence intervals) from the mixed modeling analyses of psychosocial outcomes from baseline, two weeks, and 12 months for receivers.

Variable (reference)	Outcome variables			
	IES	HADS	Perceived risk	Knowledge of familial BC and PRS
	Coefficient (95% confidence interval)			
Time 2 weeks (baseline)	-3.0 (-6.2-0.3)	0.71 (-0.50-0.94)	-10.86 (-20.24--1.48)^a	0.46 (0.06-0.86)^a
Time 12 months (baseline)	-0.9 (-4.2-2.4)	-0.30 (-1.5-0.94)	-10.23 (-19.50--1.00)^a	0.38 (-0.19-0.78)
PRS (PRS-)	-1.2 (-4.0-1.5)	0.01 (-1.03-1.05)	0.02 (-7.74-7.78)	0.31 (-0.23-0.65)
BC history (unaffected)	7.0 (4.4-9.6)^c	2.30 (1.30-2.30)^c	5.55 (0.80-10.31)^a	0.27 (-0.06-0.59)
Life events	1.4 (0.4-2.5)^a	1.49 (1.00-1.80)^c	-	-
Interaction time 1*PRS	-	-	8.4 (-3.4-20.36)	-
Interaction time 2*PRS	-	-	13.6 (1.87-25.34)^a	-
	MICRA: distress	MICRA: uncertainty	MICRA: positive response	Decisional regret
	Coefficient (95% confidence interval)			
Time 12 months (2 weeks)	0.84 (-0.23-1.91)	1.23 (-0.21-2.80)	-4.1 (-6.27--2.04)^c	-2.61 (-5.7-0.48)
PRS (PRS-)	1.61 (0.52-2.70)^a	1.40 (-0.17-2.97)	-4.33 (-6.0--2.70)^b	3.41 (0.31-6.51)^a
BC history (unaffected)	1.76 (0.71-2.81)^b	3.56 (2.05-5.07)^c	-0.02 (-1.20-1.24)	2.96 (-0.02-5.95)
Life events	0.48 (0.06-0.90)^a	1.24 (0.31)^c	-0.16 (0.27)	-
Interaction time*PRS	-	-	1.30 (-1.30-3.90)	-

BC breast cancer, HADS Hospital Anxiety and Depression Scale, IES Impact of Event Scale, MICRA Multidimensional Impact of Cancer Risk Assessment, PRS polygenic risk score.

^a $p < 0.05$.

^b $p < 0.01$.

^c $p < 0.001$.

Statistically significant results are represented in bold.

bilateral mastectomy at baseline were categorized as never screened ($n = 13$, 8.2%), distant (last screening >5 years ago; $n = 17$, 10.8%), somewhat distant (3 to 4 years ago; $n = 2$, 1.3%), and recent screening (<2 years; $n = 126$, 79.7%). Among women who reported recent screening, most had mammograms ($n = 113$, 89.7%) and/or breast ultrasounds ($n = 85$, 67.4%). Among the 27 women who had a recent breast MRI, 17 (63.0%) were aged 49 years or younger. The 13 participants who reported never having any breast screening were all unaffected and aged between 24 and 42 years.

At 12 months, 139 (81.7%) women provided information regarding their breast screening in the preceding year since receiving their PRS (receivers) or enrollment (decliners). Of these most had undertaken mammograms ($n = 96$, 93.2%) and/or breast ultrasounds ($n = 59$, 57.2%), or MRIs ($n = 14$, 8.3%). Eight women who had never been screened ($n = 1$), reported distant ($n = 6$), or somewhat distant ($n = 1$) screening undertook screening within the study period. Of these eight women, five were PRS+, two PRS-, and one decliner.

Multivariable logistic regression indicated that affected women (odds ratio [OR] = 4.9, $p = 0.025$), over the age of 40 years (OR =

8.2, $p < 0.001$), and those who had attended a familial cancer clinic prior to study enrollment (OR = 3.1, $p = 0.03$) were more likely to report having breast screening at 12 months (Table 5). There was no effect of the PRS, level of education, or number of relatives diagnosed with breast cancer on breast screening at 12 months. Overall, no evidence was found for disproportionate or clinically unjustified decisions relating to uptake of risk management strategies in the 12 months after receiving a personal PRS result.

Comparison between decliners and receivers

There were no significant differences in IES ($p = 0.07$) and HADS scores ($p = 0.86$), adjusted for baseline values between decliners and receivers at 12 months. However, decliners reported a significantly higher regret over their decision to not receive their PRS (M 37.9, SD 16.2) when compared to receivers (M 9.3; SD 15.1) ($p < 0.001$). Decliners most frequently rated the reason for not receiving their PRS as they were "happy with their lives right now" (72.0%), because they felt they were "already aware of their level of breast cancer risk" (41.7%) and "the test will not tell me when I will develop breast cancer" (36.0%) (Supplementary Table 2). In

Table 4. Uptake of bilateral mastectomy and risk-reducing medication over the course of the study, separated by personal history, PRS received, and decliners.

Participant group	Baseline		12 months		Uptake of risk-reducing strategy <i>n</i>
	No <i>n</i> (%)	Yes <i>n</i> (%)	No <i>n</i> (%)	Yes <i>n</i> (%)	
Bilateral mastectomy					
Affected/PRS+	31 (63.3)	18 (36.7)	29 (59.2)	20 (40.8)	2
Affected/PRS−	18 (69.2)	8 (30.8)	18 (69.2)	8 (30.8)	0
Unaffected/PRS+	44 (97.8)	1 (2.2)	43 (95.6)	2 (4.4)	1
Unaffected/PRS−	28 (100.0)	0 (0.0)	28 (100.0)	0 (0.0)	0
Decliners	24 (75.0)	8 (25.0)	23 (71.9)	9 (28.1)	1
Total sample	145 (80.6)	35 (19.4)	141 (78.3)	39 (21.7)	4
Risk-reducing medication					
Affected/PRS+	26 (57.8)	19 (42.2)	22 (48.9)	23 (51.1)	4
Affected/PRS−	13 (46.4)	15 (53.6)	12 (42.9)	16 (57.1)	1
Unaffected/PRS+	42 (97.7)	1 (2.3)	41 (95.3)	2 (4.7)	1
Unaffected/PRS−	28 (100.0)	0 (0.0)	28 (100.0)	0 (0.0)	0
Decliners	20 (71.4)	8 (28.6)	20 (71.4)	8 (28.6)	0
Total sample	129 (75.0)	43 (25.0)	123 (71.5)	49 (28.5)	6

PRS polygenic risk score.

Table 5. Univariate and multivariate logistic regression assessing predictors of breast screening among receivers at 12 months (*n* = 117).

Predictor variable (reference)	Univariate logistic regression		Multivariate logistic regression ^a	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
PRS received (PRS−)	2.07 (0.88– 4.85)	0.094	NS	
Personal history of breast cancer (unaffected)	5.85 (2.11– 16.23)	<0.001	4.89 (1.22–19.63)	0.025
Age at baseline (under 40 years)	9.41 (3.45– 25.64)	<0.001	8.21 (2.68–25.09)	<0.001
Level of education (did not complete bachelor's degree)	1.94 (0.80– 4.73)	0.145	-	-
Higher number of FDR or SDR with breast cancer	0.883 (0.60– 12.98)	0.525	NS	
Attended familial cancer clinic in the past (no)	3.87 (1.60– 9.37)	0.003	3.14 (1.07–9.20)	0.037

CI confidence interval, FDR first degree relatives, PRS polygenic risk score, SDR second-degree relatives.

Statistically significant results are represented in bold.

DISCUSSION

Several studies have demonstrated the potential for improved clinical outcomes from the use of a PRS for breast cancer risk [1, 3–5], however, few have described patient responses to receiving this information. Our study provides the detailed prospective examination of PROMs and risk management behavior in the year following receipt of a PRS. The findings indicate that women report minimal adverse psychological impact up to 12 months post receipt of result. Receiving a PRS was associated with adjustments in perceived breast cancer risk, which were sustained at 12 months. Persistent knowledge gaps were also identified, highlighting a need for additional educational resources to support the communication of PRS in clinical practice. Lived experiences, including personal history of breast cancer and the presence of stressful life events, proved to be strong predictors of psychological wellbeing. This finding is in line with research evaluating outcomes of *BRCA1/2* testing, which consistently reported increased distress among women with a personal history of breast cancer [30]. Together these data provide important insights into the requirements for a successful practice model that incorporates the breast cancer PRS. Such a model would need to consider the personalized nature of the PRS, and how it differs from monogenic information, while also continuing to acknowledge the importance of patients' lived experiences as a major influence on how they cope and adjust to genetic risk information.

Although it was not possible to evaluate the accuracy of perceived risk in this population, it is evident that women overestimated their level of risk (mean self-estimated lifetime risk at baseline 52%). Despite adjustments in risk perception among PRS− women at 12 months, the mean estimated absolute risk in this population remained inflated (mean 41%). This finding is consistent with previous reports that women overestimate their absolute risk of breast cancer and generally have poor numerical recall [31]. Instead women are more likely to perceive their level of risk categorically, with verbal descriptions such as “high” or “probable” [32]. In contrast to numerical estimates, women's self-categorization has also been shown to be largely consistent with estimates provided by health professionals [32, 33]. Other factors

the open-ended responses, decliners also described other concerns such as being unable to attend appointment in person, already undertaking appropriate breast cancer risk management and concerns over emotional response (Supplementary Table 3).

widely reported as influencing perceived risk include lived experiences related to cancer and emotional state to cancer [31, 32].

Based on the psychometric properties of the measures used, women in our cohort reported minimal adverse psychological outcomes post receipt of the PRS. However, compared to those with a low PRS, women with a high PRS reported greater genetic testing-specific distress, perceived risk, decisional regret and less genetic testing-positive response. These findings are in line with previous studies evaluating women's responses to *BRCA1/2* genetic testing, with women who are heterozygous for a pathogenic/likely pathogenic variant in these genes more likely to report negative psychological outcomes, compared women without a variant. Thus, as with other forms of genetic testing, our findings highlight that attention needs to be paid to psychological outcomes associated with receiving PRS, including that woman at higher genetic risk may require additional support following receipt of result.

In the first year following PRS testing the additional uptake of risk-reducing strategies in this group was low. Most women received a PRS that equated to a moderately increased risk of breast cancer (Supplementary Fig. 3) [34], and in the absence of a strong family history, this level of risk would rarely be sufficient to prompt a recommendation for risk-reducing surgery. Based on this risk, the uptake of risk-reducing bilateral mastectomy was in line with current national guidelines of breast cancer risk management. Uptake of risk-reducing salpingo oophorectomy (RRSO) was not evaluated in our study.

At baseline, most women reported regular breast screening, consistent with evidence that women continued to engage in screening despite previously receiving negative *BRCA1/2* genetic testing results [35]. To date, there is limited evidence of the impact of PRS on cancer risk management, and concerns have been raised over the potential for negative health behaviors among those receiving a low PRS [9]. Our findings indicate that although PRS—women reported significantly lower perceived risk, the PRS result was not an independent predictor of breast screening, reflecting the fact that the PRS—group of women continued to engage in screening. Previous qualitative evidence suggests that women are able to place their PRS in the context of multifactorial nature of breast cancer risk, including family history and lifestyle factors [13]. Additionally, women who receive a high PRS result reported greater awareness of their breast cancer risk and felt empowered to access appropriate risk management strategies [13]. Future studies should aim to further explore the impact of receiving PRS on motivation to have, and long-term adherence to, breast screening in a larger cohort. It is also important to highlight that there are no clinical guidelines on the use of breast cancer PRS and there is limited data on the extent in which the PRS improves clinical outcomes [1]. To address this limitation, several clinical trials of breast cancer PRS are now underway in Australia (e.g., PRiMo [36]) and internationally (e.g., WISDOM [37]). These trials will generate important data on the clinical utility of breast cancer PRS and provide a framework for the implementation of this test in clinical practice.

Very little is known about individuals who decline to receive genetic information. We identified that decliners experienced significantly greater decisional regret. Decliners also report fewer perceived benefits and greater practical and emotional concerns about receiving their PRS when compared to receivers [15]. Similar concerns have been reported across other populations including individuals notified about the availability of genetic testing for melanoma [21] and ovarian cancer risk [38]. These findings emphasize the need to continue to improve access to genetic health services. Genetic counseling for familial breast cancer is ideally placed for widespread implementation of telehealth services, with studies reporting this model to be cost effective [39] and comparable to in-person consultations. The decisional

regret reported among decliners also suggests some women may require additional support to facilitate genetic testing decisions. Tools such as decision aids can assist individuals making decisions about whether to take up genetic counseling and testing [40].

This study provides insight into the impact of a PRS-based breast cancer risk assessment on PROMs and risk management behavior over a significant period of follow-up. The study found that PRS results were acceptable with no evidence for clinically significant adverse psychological outcomes or negative effects on health behavior. However, these findings should be interpreted in light of the study limitations. There was little diversity in this cohort demographically with nearly all women born in Australia and speaking English at home. Thus, generalizability to other cultural and linguistic groups is limited. Consideration also needs to be given to the low retention rate among decliners and findings for this group of women should be interpreted with caution.

Women were also recruited from families that had previously tested negative for pathogenic variants in monogenic risk genes. Similarly, it is likely that women self-selected to participate in the study based on interest in receiving their PRS (uptake of PRS laid between 62% and 42%) [15]. As previously reported, this cohort is comprised of early adopters [15], with women who elected to receive their PRS being more likely to have completed higher level education, and reported greater benefits and fewer barriers and concerns about receiving their results than decliners. It is possible that these differences are reflected in the reported PROMs, which may not be fully representative of all women offered polygenic testing. Women also received their PRS from a genetic health professional and the findings may not be representative of women who receive PRS from other health providers and do not receive genetic counseling. Finally, with a relatively small cohort, the study was not powered to evaluate impact on risk management behavior, and findings were limited to 12-month follow-up. Nevertheless, the outcomes of the study provide insight into women's responses to receiving PRS and highlight the issues that need to be addressed in the associated model of genetic counseling. Future studies are warranted to assess clinical benefits of providing PRS including long-term adherence to breast screening, effect on health outcomes, and cost-benefit analysis.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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AUTHOR CONTRIBUTIONS

Conceptualization: T.Y., B.M., M.A.Y., K.B.S., Y.A., P.J. Data curation: T.Y., B.M., R.K., M.S.J., S.M. Formal Analysis: T.Y., B.M., R.K., B.B.S., P.J. Funding acquisition: TY, B.M., M.A.Y., K.B.S., Y.A., P.J. Investigation: T.Y., B.M., R.K., M.A.Y., P.B.M., M.S.J., S.M., S.T., K.B.S., Y.A., L.S., C.S., B.B.S., P.A.J. Methodology: T.Y., B.M., M.A.Y., K.B.S., Y.A., P.J. Project administration: B.M., M.A.Y., K.B.S. P.J. Supervision: B.M., M.A.Y., K.B.S. P.J. Validation: B.M., M.A.Y., K.B.S. P.J. Visualization: T.Y., B.M., M.A.Y., K.B.S. P.J. Writing—original draft: T.Y., B.M. Writing—review & editing: T.Y., B.M., R.K., M.A.Y., P.B.M., M.S.J., S.M., S.T., K.B.S., Y.A., L.S., C.S., B.B.S., P.A.J.

ETHICS DECLARATION

The study was approved by the Human Research Ethics Committee at participating sites (HREC/16/PMCC/2 and H0016395). Informed consent was obtained for each enrolled study participant.

COMPETING INTERESTS

B.M. has a remunerated consultant role with the company AstraZeneca with respect to an unrelated project. AstraZeneca has not been involved in the collection or analysis of data for articles nor in writing or submitting the manuscript. The other authors declare no competing interests.

ADDITIONAL INFORMATION

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